MAJOR ARTICLE

Antimicrobial-Resistant Nontyphoidal *Salmonella* Is Associated with Excess Bloodstream Infections and Hospitalizations

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Background. Nontyphoidal *Salmonella* is a leading cause of foodborne illness. Few studies have explored the health consequences of antimicrobial-resistant *Salmonella.*

Methods. The National Antimicrobial Resistance Monitoring System (NARMS) performs susceptibility testing on nontyphoidal *Salmonella* isolates. The Foodborne Diseases Active Surveillance Network (FoodNet) ascertains outcomes for patients with culture-confirmed *Salmonella* infection, in 9 states, each of which participates in NARMS. We analyzed the frequency of bloodstream infection and hospitalization among patients with resistant infections. Isolates defined as resistant to a clinically important agent were resistant to 1 or more of the following agents: ampicillin, ceftriaxone, ciprofloxacin, gentamicin, and/or trimethoprim-sulfamethoxazole.

Results. During 1996–2001, NARMS received 7370 serotyped, nontyphoidal *Salmonella* isolates from blood or stool. Bloodstream infection occurred more frequently among patients infected with an isolate resistant to $\geq$1 clinically important agent (adjusted odds ratio [OR], 1.6; 95% confidence interval [CI], 1.2–2.1), compared with patients with pansusceptible infection. During 1996–2001, FoodNet staff ascertained outcomes for 1415 patients who had isolates tested in NARMS. Hospitalization with bloodstream infection occurred more frequently among patients infected with an isolate resistant to $\geq$1 clinically important agent (adjusted OR, 3.1; 95% CI, 1.4–6.6), compared with patients with pansusceptible infection.

Conclusions. Patients with antimicrobial-resistant nontyphoidal *Salmonella* infection were more likely to have bloodstream infection and to be hospitalized than were patients with pansusceptible infection. Mitigation of antimicrobial resistance in *Salmonella* will likely benefit human health.

Infection with nontyphoidal *Salmonella* causes illness in ~1.4 million patients annually in the United States [1]. Most infections result in acute gastroenteritis and do not require antimicrobial therapy. However, antimicrobial agents are commonly prescribed for patients with salmonellosis, particularly those patients at high risk of extraintestinal infection, including the very young, the very old, and those with immune suppression [2]. For patients with extraintestinal infection, such as bacteremia or meningitis, antimicrobial therapy may be life saving [3].

Over the past several decades, the prevalence of antimicrobial-resistant *Salmonella* has increased [4–7]. In 1980, for example, 13% of *Salmonella* serotype Typhimurium isolates, the most common *Salmonella* serotype isolated from humans in the United States, were resistant to $\geq$1 of 9 antimicrobial agents; by 2001, this proportion had increased to 51% [7]. In the 1990s, a

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strain of *Salmonella* Typhimurium resistant to ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline (R-type ACSSuT) emerged in the United States and Europe; most isolates were definitive phage type 104 (DT104) [8]. In 2001, R-type ACSSuT *Salmonella* Typhimurium accounted for 7% of nontyphoidal *Salmonella* isolates tested in US national public health surveillance [7].

Historically, physicians prescribed ampicillin and chloramphenicol to patients with acute abdominal syndromes or to patients at high risk of complications from bacterial gastroenteritis. Over time, use of other agents, including gentamicin, trimethoprim-sulfamethoxazole, fluoroquinolones (e.g., ciprofloxacin), and third-generation cephalosporins (e.g., ceftriaxone), became more common [3]. Resistance to these agents is less frequent [7]. As part of its Healthy People 2010 objectives, the US Department of Health and Human Services (Washington, DC) has set targets for controlling *Salmonella* resistance to ampicillin, gentamicin, fluoroquinolones, and third-generation cephalosporins in infection in humans [9].

In the United States, a large majority of nontyphoidal *Salmonella* infections are caused by contaminated food [1]. Several lines of evidence demonstrate that the use of antimicrobial agents in food animals contributes to the emergence and dissemination of antimicrobial resistance in foodborne *Salmonella* [10]. Few studies, however, have explored the consequences for human health of increasing *Salmonella* resistance. Although rare, treatment failure has been documented for infection caused by antimicrobial-resistant nontyphoidal *Salmonella* [11]. Studies of other human health outcomes, such as hospitalization and bloodstream infection, have become possible only recently in the United States, with the establishment of national laboratory-based surveillance systems. We analyzed data from 2 national surveillance systems, to determine whether infections caused by antimicrobial-resistant nontyphoidal *Salmonella* were more likely to result in bloodstream infection and hospitalization than were antimicrobial-susceptible infections.

MATERIALS AND METHODS

National Antimicrobial Resistance Monitoring System (NARMS) for enteric bacteria. In the United States, clinical laboratories are requested and, in some states, required to send all *Salmonella* isolates to their respective state public health laboratories for serotyping. Since the establishment of NARMS (http://www.cdc.gov/narms) in 1996, participating state public health laboratories have forwarded every 10th nontyphoidal *Salmonella* isolate, regardless of specimen source or serotype, to the Centers for Disease Control and Prevention (CDC; Atlanta) for susceptibility testing. In 2001, the population under surveillance in the 17 NARMS-participating states included 109 million persons, which was 40% of the US population [7]. A log sheet that records each patient's age, county of residence, and sex; the source of specimen collection; and the state-laboratory isolate identification number is submitted together with the isolates. Only 1 isolate from each patient is accepted per year.

Isolates received at the CDC undergo susceptibility testing with a semiautomated system (Sensititre; TREK Diagnostic Systems). From 1996 to 2001, the partial range MIC was determined for the following 14 antimicrobial agents: amikacin, ampicillin, amoxicillin–clavulanic acid, ceftriaxone, cephalothin, chloramphenicol, ciprofloxacin, gentamicin, kanamycin, nalidixic acid, streptomycin, sulfamethoxazole, tetracycline, and trimethoprim-sulfamethoxazole. Isolates that met screening criteria for possible ceftriaxone resistance, as determined by Sensititre, were tested with the E-test system (AB Biodisk) from 1996 to 1998 and by manual broth microdilution from 1999 to 2001, to confirm ceftriaxone-susceptibility results. National Committee for Clinical Laboratory Standards interpretive criteria were used [12]. MIC results were dichotomized; isolates with decreased susceptibility were categorized as "sensitive."

The Foodborne Diseases Active Surveillance Network (FoodNet). The CDC's FoodNet (http://www.cdc.gov/foodnet) has conducted laboratory-based surveillance of *Salmonella* since 1996, by recording standardized data for all patients with infection confirmed at any of the >450 clinical laboratories in the surveillance area. In 2001, the population in the 9 FoodNet surveillance sites was 38 million persons, which was 13% of the US population [13]. Data collected included patient age, sex, race, ethnicity, and county of residence; state-laboratory isolate identification number; mortality within 30 days after specimen collection; hospitalization status within 7 days after specimen collection; and length of hospital stay, if any.

Analysis. We conducted 2 analyses. First, we analyzed NARMS data for 1996–2001, to determine the frequency of bloodstream infection among patients with resistant *Salmonella* infection, compared with patients with pansusceptible infection. Second, we linked cases from NARMS to FoodNet by use of the state-laboratory isolate identification number and determined the frequency of hospitalization and bloodstream infection among patients with resistant and those with pansusceptible *Salmonella* infection. By definition, patients in this FoodNet/NARMS analysis lived in the surveillance areas of both systems, developed a culture-confirmed nontyphoidal *Salmonella* infection during 1996–2001, had a completed FoodNet case-report form, and had an isolate forwarded to NARMS as part of the 10% of isolates sent to the CDC. Records that could not be linked because of missing or discordant identifying information were excluded from the FoodNet/NARMS analysis. In both analyses, "clinically important resistance" was defined as resistance to 1 or more of the following agents: ampicillin, ceftriaxone, ciprofloxacin, gentamicin, and/or trimethoprim-sulfamethoxazole.

Variables were included in statistical models if they were

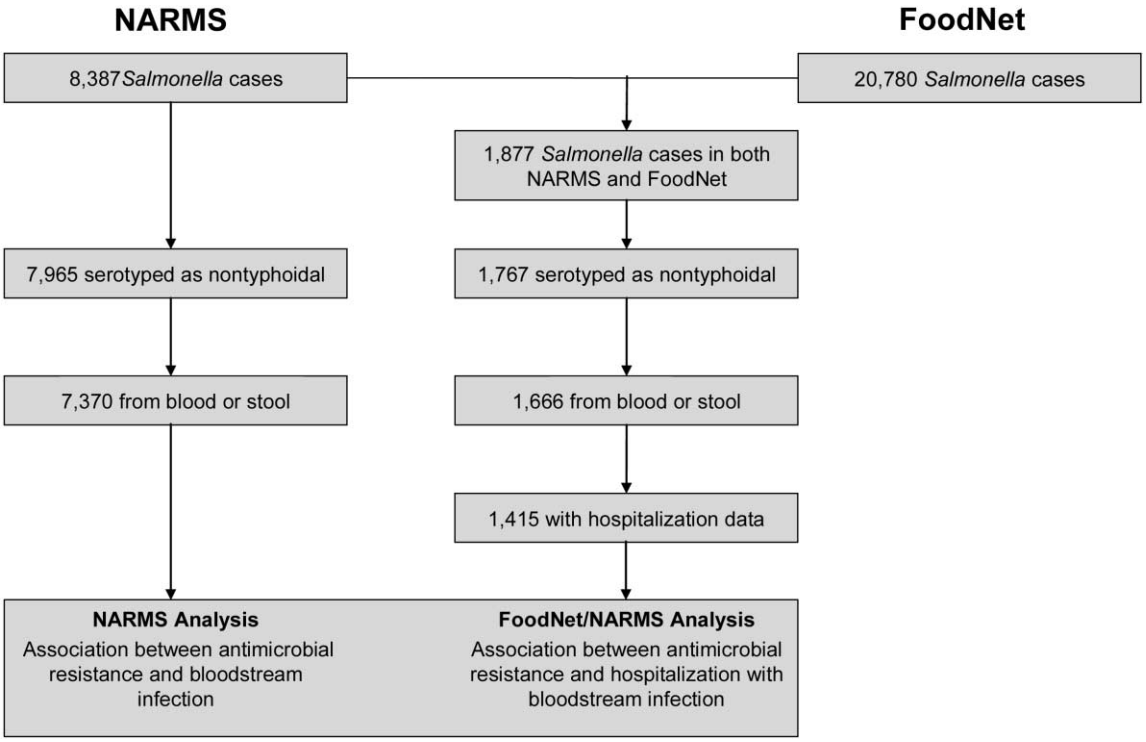

Figure 1. Patients with culture-confirmed *Salmonella* infection ascertained by surveillance and included in analyses of data from the National Antimicrobial Resistance Monitoring System (NARMS) and the Foodborne Diseases Active Surveillance Network (FoodNet), 1996–2001.

known or believed to be associated with antimicrobial resistance and either bloodstream infection or hospitalization. These variables included age, sex, race, and *Salmonella* serotype. In the NARMS analysis, data on race were not available, and serotype was a categorical variable, with 50 common serotypes included individually and less-common serotypes classified as "other." In the FoodNet/NARMS analysis, only 4 serotypes were included in the model; all other serotypes were classified as "other." In both analyses, *Salmonella* Typhimurium was used as the referent. Because of a high prevalence of resistance among *Salmonella* Typhimurium isolates, we also performed a subset analysis restricted to this serotype.

For continuous variables, medians were compared by use of the Wilcoxon rank sum test. For categorical variables, proportions were compared by use of the χ^2 test. Significance was defined as $P < .05$. In the NARMS analysis of bloodstream infection, we used logistic regression to model the effect of covariates on outcomes. For the FoodNet/NARMS analysis of hospitalization, in which the outcome contained multiple strata (e.g., outpatient, hospitalization with intestinal infection, or hospitalization with bloodstream infection), we used polytomous logistic regression [14]. All data were analyzed by SAS (version 9.0; SAS Institute). This study was exempt from approval by institutional review boards, because it used existing, anonymous data collected as part of public health surveillance.

RESULTS

NARMS analysis. From 1996 to 2001, NARMS-participating public health laboratories forwarded *Salmonella* isolates from 8387 patients to the CDC. We analyzed data from the 7370 isolates (88%) that were serotyped as nontyphoidal and that were from blood or stool (figure 1). Among these, the most common *Salmonella* serotypes were Typhimurium (26%), Enteritidis (23%), and Newport (7%). The median age of patients was 20 years (interquartile range [IQR], 3–41 years), and 3526 patients (48%) were female. Bloodstream infection occurred in 443 patients (6%). A total of 4490 isolates (61%) were susceptible to all antimicrobial agents tested (i.e., were pansusceptible) (table 1). In the univariate analysis, isolates resistant to $\geq$1 antimicrobial agent or $\geq$1 clinically important agent were more likely to be from blood than were pansusceptible isolates (table 2). Some serotypes were associated with an increased frequency of bloodstream infection. Bloodstream infections also were more common among patients $\geq$65 years of age and among male patients.

In the multivariate analysis adjusted for *Salmonella* serotype and patient age and sex, patients with resistant infection were more likely to have a bloodstream infection, compared with patients with pansusceptible infection (table 3). When we restricted the multivariate analysis to the 1880 patients infected

Table 1. Frequency of resistance to antimicrobial agents among *Salmonella* isolates tested in the National Antimicrobial Resistance Monitoring System (NARMS; $n = 7370$) and in a Foodborne Diseases Active Surveillance Network (FoodNet)/NARMS analysis ($n = 1415$).

Antimicrobial agent or pattern of antimicrobial resistance	No. (%) of resistant isolates	
	NARMS	FoodNet/NARMS
Agent		
Amikacin	1 (0.01)	0 (0)
Ampicillin	1311 (18)	272 (19)
Amoxicillin–clavulanic acid	198 (3)	47 (3)
Ceftriaxone	93 (1)	25 (2)
Cephalothin	264 (4)	52 (4)
Chloramphenicol	765 (10)	181 (13)
Ciprofloxacin	6 (0.1)	0 (0)
Gentamicin	221 (3)	37 (3)
Kanamycin	383 (5)	81 (6)
Nalidixic acid	90 (1)	16 (1)
Streptomycin	1379 (19)	307 (22)
Sulfamethoxazole	1499 (20)	321 (23)
Tetracycline	1545 (21)	327 (23)
Trimethoprim-sulfamethoxazole	172 (2)	25 (2)
Pattern		
Pansusceptible	4490 (61)	886 (63)
⩾1 Agent	2880 (39)	529 (37)
Clinically important[a]	1495 (20)	306 (22)
R-type ACSSuT[b]	684 (9)	169 (12)

NOTE. Proportions are similar in both groups because the FoodNet/NARMS data set was a sample of the NARMS data set.

[a] Resistant to at least ampicillin, ceftriaxone, ciprofloxacin, gentamicin, or trimethoprim-sulfamethoxazole.

[b] Resistant to at least ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline.

with *Salmonella* Typhimurium, patients with resistant infection were even more likely to have a bloodstream infection, compared with patients with pansusceptible infection. A total of 23 (3%) of 742 patients with infection caused by pansusceptible *Salmonella* Typhimurium isolates had a bloodstream infection, compared with 69 (6%) of 1138 patients with infection caused by isolates resistant to ⩾1 antimicrobial agent. After adjustment for age and sex, the multivariate odds ratios (ORs) were 2.1 (95% confidence interval [CI], 1.3–3.5) for resistance to ⩾1 antimicrobial agent, 2.4 (95% CI, 1.5–4.0) for resistance to ⩾1 clinically important agent, and 2.5 (95% CI, 1.5–4.4) for R-type ACSSuT.

FoodNet/NARMS analysis. From 1996 to 2001, FoodNet-participating state public health departments submitted case-report forms for 20,780 patients with *Salmonella* infection (figure 1). The public health laboratories in these states, in accordance with the NARMS surveillance protocol, randomly selected 1877 isolates (9%) from these patients and forwarded them to the CDC for standardized antimicrobial-susceptibility testing. Of these, 1666 isolates were grown from either blood or stool samples and were serotyped as nontyphoidal. We analyzed data for 1415 isolates (85%) for which information regarding whether the patient had been hospitalized within 7 days of specimen collection was available in FoodNet. Among these 1415 isolates, the most common *Salmonella* serotypes were Typhimurium (31%), Enteritidis (20%), and Heidelberg (8%). The median age of patients was 24 years (IQR, 4–41 years), and 691 patients (49%) were female. Race was reported for 984 patients (70%); of these, 225 patients (23%) were nonwhite. Hospitalization had occurred for 346 patients (25%). Of the 1415 isolates, 93 (7%) were from blood. Of 93 patients with bloodstream infection, 56 (60%) had been hospitalized; of 1322 patients with intestinal infection, 290 (22%) had been hospitalized. A total of 886 isolates (63%) were pansusceptible (table 1).

In the univariate analysis, patients infected with resistant isolates were slightly more likely to be hospitalized than were patients infected with pansusceptible isolates: the ORs were 1.3 (95% CI, 1.0–1.6) for resistance to ⩾1 antimicrobial agent, 1.3 (95% CI, 1.0–1.7) for resistance to ⩾1 clinically important agent, and 1.3 (95% CI, 0.9–1.7) for R-type ACSSuT.

Among hospitalized patients, those infected with resistant isolates had a longer hospital stay than did those infected with pansusceptible isolates. The median hospital stay was 3 days for 191 patients hospitalized with susceptible infection, compared with a median hospital stay of 4 days for patients with resistant infection ($n = 138$ and $P = .02$, for resistance to ⩾1 antimicrobial agent; $n = 79$ and $P = .01$, for resistance to ⩾1 clinically important agent; and $n = 43$ and $P = .03$, for R-type ACSSuT).

Data on mortality within 30 days after specimen collection were available for 1242 patients (88%); 8 patients (0.6%) had died. Of the 8 patients who had died, 6 (75%) had been hospitalized with bloodstream infection due to *Salmonella* Typhimurium, and 2 (25%) had been hospitalized with intestinal infection due to *Salmonella* Enteritidis. Three of the *Salmonella* Typhimurium isolates were R-type ACSSuT, and 3 were pansusceptible. Both *Salmonella* Enteritidis isolates were pansusceptible.

Because our analysis of NARMS data showed that antimicrobial resistance was associated with bloodstream infection, we extended the FoodNet/NARMS univariate analysis and found that antimicrobial resistance was associated with an increased frequency of hospitalization with bloodstream infection (table 4). In contrast, antimicrobial resistance was not associated with an increased rate of hospitalization with intestinal infection (ORs were 1.1 [95% CI, 0.9–1.5] for resistance to ⩾1 antimicrobial agent, 1.2 [95% CI, 0.8–1.8] for resistance to ⩾1 clinically important agent, and 1.1 [95% CI, 0.7–1.7] for R-type ACSSuT). When we restricted the univariate analysis to the 437 patients with *Salmonella* Typhimurium infection, we

Table 2. Univariate analysis of the frequency of *Salmonella* isolates from blood, among patients who had isolates submitted to the National Antimicrobial Resistance Monitoring System ($n = 7370$), 1996–2001.

Variable	No. of isolates	No. (%) of isolates from blood	OR (95% CI), for bloodstream infection[a]
Salmonella serotype			
Typhimurium	1880	92 (5)	Referent
Enteritidis	1661	122 (7)	1.5 (1.2–2.1)
Newport	494	4 (1)	0.2 (0.1–0.4)
Heidelberg	468	62 (13)	3.0 (2.1–4.2)
Javiana	226	5 (2)	0.4 (0.2–1.1)
Montevideo	192	5 (3)	0.5 (0.2–1.3)
Thompson	162	6 (4)	0.8 (0.3–1.7)
München	161	1 (1)	0.1 (0.0–0.9)
Oranienburg	144	17 (12)	2.6 (1.5–4.5)
Saintpaul	139	5 (4)	0.7 (0.3–1.8)
Sandiego	33	10 (30)	8.5 (3.9–18.3)
Dublin	20	16 (80)	77.7 (25.5–237.2)
Other	774	26 (5)	0.7 (0.4–1.1)
Age of patient			
18–64 years	2835	183 (7)	Referent
<1 years	641	38 (6)	0.9 (0.6–1.3)
1–4 years	1336	54 (4)	0.6 (0.4–0.8)
5–17 years	1135	43 (4)	0.6 (0.4–0.8)
65–84 years	482	61 (13)	2.1 (1.5–2.9)
⩾85 years	80	10 (13)	2.1 (1–4.1)
Sex of patient			
Female	3526	185 (5)	Referent
Male	3422	235 (7)	1.3 (1.1–1.6)
Pattern of antimicrobial resistance			
Pansusceptible	4490	254 (6)	Referent
⩾1 Agent	2880	189 (7)	1.2 (1.0–1.4)
Clinically important[b]	1495	112 (8)	1.4 (1.1–1.7)
R-type ACSSuT[c]	684	44 (6)	1.2 (0.8–1.6)

NOTE. CI, confidence interval; OR, odds ratio.

[a] Compared with intestinal infection.

[b] Resistant to at least ampicillin, ceftriaxone, ciprofloxacin, gentamicin, or trimethoprim-sulfamethoxazole.

[c] Resistant to at least ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline.

found that patients with resistant infection were even more likely to be hospitalized with bloodstream infection. Of 175 patients with pansusceptible infection, 3 (2%) had been hospitalized with bloodstream infection, compared with 17 (7%) of 262 patients with infection resistant to ⩾1 antimicrobial agent (OR, 4.3; 95% CI, 1.2–14.9), 13 (6%) of 210 patients with infection resistant to ⩾1 clinically important agent (OR, 4.1; 95% CI, 1.2–14.7), and 9 (6%) of 146 patients with infection that was R-type ACSSuT (OR, 4.0; 95% CI, 1.1–15.1).

In the multivariate analysis adjusted for *Salmonella* serotype and patient age, sex, and race, patients with resistant infection were more likely to be hospitalized with bloodstream infection, compared with patients with pansusceptible infection (table 3). Because of small numbers, adjusted ORs could not be calculated for the subset of patients with *Salmonella* Typhimurium infection only.

DISCUSSION

We found that antimicrobial resistance in nontyphoidal *Salmonella* was associated with an increased frequency of bloodstream infection and hospitalization among patients. Among the subset of patients with the most common serotype, *Salmonella* Typhimurium, the association between resistance, bloodstream infection, and hospitalization was particularly strong.

Bloodstream infection is a severe complication of salmonellosis, potentially resulting in sepsis, endocarditis, meningitis, septic metastases, and death [15]. If antimicrobial-resistant in-

Table 3. Multivariate analysis of the frequency of *Salmonella* isolates from blood, among patients who had isolates submitted to the National Antimicrobial Resistance Monitoring System (NARMS; $n = 7370$), and the frequency of hospitalization with bloodstream infection, among patients ascertained in the Foodborne Diseases Active Surveillance Network (FoodNet) from among those in NARMS ($n = 1415$), 1996–2001.

	OR (95% CI)	
Pattern of antimicrobial resistance	For bloodstream infection,[a] in NARMS analysis	For hospitalization with bloodstream infection,[b] in FoodNet/NARMS analysis
Pansusceptible	Referent	Referent
⩾1 Agent	1.2 (1.0–1.5)	1.7 (0.9–3.1)
Clinically important[c]	1.6 (1.2–2.1)	3.1 (1.4–6.6)
R-type ACSSuT[d]	2.1 (1.3–3.3)	4.6 (1.3–16.7)

NOTE. CI, confidence interval; OR, odds ratio.

[a] Compared with intestinal infection.

[b] Compared with not hospitalized.

[c] Resistant to at least ampicillin, ceftriaxone, ciprofloxacin, gentamicin, or trimethoprim-sulfamethoxazole.

[d] Resistant to at least ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline.

fection increases the risk of bloodstream infection, as our results suggest, then the human-health consequences of increasing resistance may be substantial. Although we did not collect data on the indication for hospitalization of individual patients, our finding that patients with resistant infection were hospitalized more frequently with bloodstream infection and for longer periods of time suggests substantial excess cost in health-care expenditures and lost productivity.

Our results confirm and extend findings from previous studies. Lee et al. [6] and Holmberg et al. [16, 17] identified an association between resistant *Salmonella* and excess hospitalization, in data from national surveillance and outbreak investigations, respectively, in the United States. By studying data for a larger number of patients, from 2 national surveillance systems, and by including data on *Salmonella* serotype, we were able to identify bloodstream infection as a possible reason for the rate of excess hospitalization. The association between resistance, hospitalization, and bloodstream infection was greatest for *Salmonella* Typhimurium, which supports findings from studies conducted in Canada by Martin et al. [19] and in Denmark by Mølbak et al. [11] and Helms et al. [18]. One study in England did not find an association between multidrug-resistant *Salmonella* Typhimurium DT104 and bloodstream infection [20]. Helms et al. [18] also identified a markedly increased mortality rate within 2 years after infection with nalidixic acid–resistant *Salmonella* Typhimurium. Nalidixic acid, although not used clinically, is an elementary quinolone. Nalidixic acid–resistant *Salmonella* isolates also have decreased susceptibility to ciprofloxacin and respond less well to fluoroquinolone treatment, compared with susceptible isolates [7, 21]. Results from our study were similar when we expanded the definition of clinically important resistance to include resistance to nalidixic acid (data not shown).

We do not know the biological or clinical mechanisms that link resistance with bloodstream infection and hospitalization. Resistance can cause or exacerbate illness through a variety of mechanisms [22]. Patients infected with resistant *Salmonella* may experience failure of empirical antimicrobial therapy. Failure of therapy may result in more-invasive illness, thereby increasing the likelihood that a resistant strain will be detected in blood. Reduced efficacy of early empirical treatment also may prompt a physician to hospitalize a patient because symptoms persist or other medical complications arise. Patients also may develop more-severe disease if the resistant *Salmonella* isolates possess additional virulence factors that enhance invasiveness or cause more-severe clinical symptoms. Alternatively, persons may develop *Salmonella* infection after receiving antimicrobial therapy for an unrelated medical condition, when the strain of *Salmonella* is resistant to the antimicrobial agent being taken; these patients may represent more-vulnerable subsets of the population. This mechanism could increase the total number of *Salmonella* infections, particularly among those who already have an illness requiring antimicrobial therapy.

Our data show an association between resistance and hospitalization with bloodstream infection but not between resistance and hospitalization with intestinal infection. This finding suggests that patients with resistant infection are hospitalized more frequently because they are more likely to have invasive infection and that the reason for the increased rate of hospitalization may be more closely related to pathogen-specific factors than to host-specific factors. If comorbid medical conditions among patients were the primary reason for hospitalization, we would have expected the rate of hospitalization with an intestinal infection to be similar to the rate of hospitalization with a bloodstream infection, when stratified by susceptibility pattern.

Our study had limitations. First, we studied only a fraction of patients with *Salmonella* infection in the United States. Only 1 in 38 patients infected with nontyphoidal *Salmonella* is reported to public health agencies [1]. Because of the NARMS sampling scheme, isolates from only a subset of patients with culture-confirmed infection reported to FoodNet undergo standardized susceptibility testing. Patients with data in these surveillance systems may differ from patients with *Salmonella* infection not reported to public health agencies. Second, we collected only limited data about cases in the surveillance systems. We did not know the indication for hospitalization, including whether patients hospitalized with bloodstream infection were hospitalized for this indication. We did not have data regarding comorbid medical conditions or prior use of antimicrobial agents. The subset of patients hospitalized with

Table 4. Univariate analysis of the frequency of hospitalization with *Salmonella* bloodstream infection, among patients ascertained in the Foodborne Diseases Active Surveillance Network who had isolates submitted to the National Antimicrobial Resistance Monitoring System ($n = 1415$), 1996–2001.

Variable	No. of patients	No. (%) of patients hospitalized with bloodstream infection	OR (95% CI), for hospitalization with bloodstream infection[a]
Salmonella serotype			
Typhimurium	437	20 (5)	Referent
Enteritidis	280	13 (5)	1.0 (0.5–2.0)
Heidelberg	111	8 (7)	1.9 (0.8–4.5)
Infantis	27	2 (7)	1.8 (0.4–8.5)
Other	560	13 (2)	0.5 (0.2–1.0)
Age of patient years			
18–64 years	702	37 (5)	Referent
0–4 years	361	10 (2)	0.5 (0.3–1.1)
5–17 years	237	4 (2)	0.3 (0.1–0.8)
65–84 years	96	3 (3)	0.8 (0.2–2.6)
⩾85 years	19	2 (11)	5.7 (1.1–30.6)
Sex of patient			
Female	691	23 (3)	Referent
Male	649	32 (5)	1.5 (0.9–2.5)
Race of patient			
White	759	20 (3)	Referent
Nonwhite	225	28 (12)	5.2 (2.8–9.5)
Pattern of antimicrobial resistance			
Pansusceptible	886	28 (3)	Referent
⩾1 Agent	529	28 (5)	1.8 (1.0–3.0)
Clinically important[b]	306	21 (7)	2.3 (1.3–4.2)
R-type ACSSuT[c]	169	11 (7)	2.2 (1.1–4.5)

NOTE. CI, confidence interval; OR, odds ratio.

[a] Compared with not hospitalized.

[b] Resistant to at least ampicillin, ceftriaxone, ciprofloxacin, gentamicin, or trimethoprim-sulfamethoxazole.

[c] Resistant to at least ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline.

bloodstream infection may have been more likely than other patients to have comorbid conditions and to have taken antimicrobial agents more frequently, the effect of which would be to increase this group's risk of hospitalization, of antimicrobial-resistant *Salmonella* infection, and, possibly, of bloodstream infection. Previous studies have indicated that patients with underlying illnesses are more likely to acquire *Salmonella* infection, but data regarding whether they are more likely than healthy patients to acquire antimicrobial-resistant *Salmonella* infection are conflicting [6, 18, 23]. Even if the association we found was driven by a single, unique patient subgroup, the net impact of excess hospitalization and bacteremia on the healthcare system would remain the same.

We do not believe that our findings are an artifact of laboratory-based surveillance. In NARMS, isolates are selected by use of systematic sampling, regardless of specimen source or susceptibility pattern; in fact, the susceptibility pattern is seldom known at the time an isolate is forwarded to the CDC. In FoodNet, patients hospitalized with *Salmonella* infection are more likely to be detected by surveillance than are patients with *Salmonella* infection who are not hospitalized, but susceptibility data are seldom known and are never recorded in FoodNet; therefore, the proportion of patients hospitalized should be the same, regardless of antimicrobial-susceptibility pattern. Patients with intestinal infection may have had bloodstream infection that either was not diagnosed or was not detected by surveillance; such misclassification should be unrelated to antimicrobial resistance.

Rates of hospitalization and bloodstream infection were markedly elevated among patients with multidrug-resistant *Salmonella* Typhimurium infection. This underscores the public health importance of DT104 and other clones associated with multidrug resistance. Nevertheless, we do not believe that our findings can be explained entirely by a single *Salmonella* clone. In NARMS, from 1997 to 1998, 65% of *Salmonella* Typhimurium isolates that were R-type ACSSuT were phage type DT104; the remainder of the isolates with this resistance pattern were distributed across 6 different phage types [24]. A recent

study from Canada found that resistance pattern, not phage type, was the main risk factor for hospitalization of patients infected with resistant *Salmonella* Typhimurium [19]. Moreover, our findings remained significant, even after the analysis was controlled for serotype. Sample size restricted us from performing a subset multivariate analysis for isolates other than *Salmonella* Typhimurium. Our study confirmed that serotype is an important predictor of bloodstream infection [25]. Similar subset analyses for other serotypes would be useful.

This study presents new evidence of the public health implications of antimicrobial resistance, on the basis of data collected prospectively over several years from 2 large surveillance systems. Because the major reservoir of nontyphoidal *Salmonella* is in food animals, the emergence of resistance in nontyphoidal *Salmonella* is primarily a consequence of selective pressure associated with the use of antimicrobial agents in food animals [10, 26, 27]. Policies that reduce the antimicrobial resistance of *Salmonella* are likely to benefit human health.

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